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(54) Title: HALOGENATED- α,β -UNSATURATED- β -(SUBSTITUTED-AMINO) CARBOXYLATE ESTERS

(57) Abstract: A process for preparing a halogenated aliphatic- α,β -unsaturated- β -nucleophile-functionalized carboxylate ester having the formula: $R^1-C(-Nu)=CH-COOR^8$ by reacting a nucleophile with a halogenated aliphatic- α,β -unsaturated- β halocarboxylate ester having the formula: $R^1-CX^1=CH-COOR^8$, wherein R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups; Nu is a nucleophile moiety different from X^1 ; X^1 is F, Cl or Br; and R^8 is selected from the group consisting of straight chain and branched C_1 - C_6 alkyl groups. Halogenated aliphatic- α,β -unsaturated- β -nucleophile-functionalized carboxylate esters, halogenated aliphatic- α,β -unsaturated- β -halocarboxylate esters, and intermediate compounds and processes in the preparation thereof are also disclosed.

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5 HALOGENATED- α,β -UNSATURATED- β - (SUBSTITUTED-AMINO)
CARBOXYLATE ESTERS

FIELD OF THE INVENTION

10 The present invention is directed to the synthesis of esters of halogenated- α,β -unsaturated- β -aminoalkanoic acids, and in particular to the synthesis of 3-(substituted-amino)-4,4,4-trifluorocrotonate esters. More specifically, the present invention is directed to the synthesis of alkyl halogenated- α,β -unsaturated- β - (substituted-amino) carboxylate esters, such as alkyl 3-methylamino-4,4,4-trifluorocrotonate, prepared by
15 the reaction of methylamine with alkyl esters of halogenated- α,β -unsaturated- β -haloalkanoic acids in a sequence of steps using a halofluorocarbon as a starting material.

DESCRIPTION OF THE PRIOR ART

20 Alkyl 3-(monosubstituted-amino)-4,4,4-trifluorocrotonates, and alkyl 3-(disubstituted-amino)-4,4,4-trifluorocrotonates are commercially useful intermediate compounds used in pharmaceutical and agricultural applications to manufacture, among other things, heterocycles, including substituted-methyl nitrogen-heterocycles. In a reaction typical of commercial applications, an alkyl 3-methylamino-4,4,4-
25 trifluorocrotonate undergoes cyclization to a trifluoromethylated-N-methylated heterocycle such as 6-trifluoromethyl-1-methyluracil.

The presently known commercial processes for the synthesis of alkyl 3-(substituted-amino)-4,4,4-trifluorocrotonates use alkyl trifluoroacetoacetates as starting materials. EP 808,826 discloses a method for preparing 3-amino-4,4,4-trihaloacetoacetates and their derivatives from a trihaloacetoacetate, or its analogs, in a
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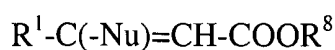
two step method consisting of: i) converting ethyl trifluoroacetoacetate to the ammonium salt $[\text{CF}_3\text{-C}(\text{O}^-)=\text{COO-C}_2\text{H}_5] [\text{NH}_4^+]$ and ii) thermolyzing the ammonium salt to ethyl 3-amino-4,4,4-trifluorocrotonate in a subsequent step. WO 99/24,390 discloses a similar preparation of $[\text{CF}_3\text{-C}(\text{O}^-)=\text{COO-C}_2\text{H}_5] [\text{CH}_3\text{NH}_3^+]$ and thermolyzing this methylammonium salt to ethyl 3-methylamino-4,4,4-trifluorocrotonate in a subsequent step. US 6,207,830, discloses the conversion of ethyl 3-methylamino-4,4,4-trifluorocrotonate to a 1-methyl-6-trifluoromethyluracil derivative.

A major shortcoming of all currently used processes for the production of alkyl 3-methylamino-4,4,4-trifluorocrotonates and related species is that the starting material, alkyl trifluoroacetoacetate, is expensive and of limited commercial availability. For this reason, it is desirable to have an alternate process for the synthesis of an alkyl 3-(substituted-amino)-4,4,4-trifluorocrotonate that does not use an alkyl trifluoroacetoacetate as starting material.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

This need is met by the present invention. The present invention provides a novel approach for the synthesis of an alkyl halogenated- α,β -unsaturated- β -(substituted-amino) carboxylate esters of formula $\text{R}^1\text{-C}(-\text{NR}^9\text{R}^{10})=\text{CH-COOR}^8$ based upon the use of halofluorocarbons as starting material. This is particularly advantageous for the economical production of alkyl 3-methylamino-4,4,4-trifluorocrotonates.

According to one aspect of the present invention, a process is provided for preparing a halogenated aliphatic- α,β -unsaturated- β -nucleophile-functionalized carboxylate ester having the formula:



wherein the process includes the step of reacting a nucleophile with a halogenated aliphatic- α,β -unsaturated- β -halocarboxylate ester having the formula:



5 wherein R^1 is selected from straight chain and branched halogenated C_1 - C_{12} aliphatic groups;

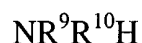
Nu is a nucleophile moiety;

X^1 is F, Cl or Br; and

R^8 is selected from straight chain and branched C_1 - C_6 alkyl groups.

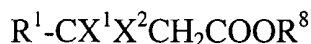
R^1 is preferably polyhalogenated, more preferably polyfluorinated and most preferably perfluorinated.

Examples of nucleophiles include, but are not limited to, anionic species such as the halide ions F^- , Cl^- , Br^- and I^- , alkoxide ions, phenoxide ions, substituted phenoxide ions, alkylamide ions, thiolate ions, acyloxy ions, cyanide, azide, cyanate ions, 15 thiocyanate ions, and the like, and neutral species, such as straight chain, branched or cyclic C_1 - C_6 alkyl alcohols and thiols, arylthiols, and the like. A particularly preferred group of nucleophilic species are amine compounds having the formula:



20 wherein R^9 and R^{10} are independently selected from hydrogen and straight chain or branched C_1 - C_6 alkyl. These produce halogenated aliphatic- α,β -unsaturated- β -nucleophile-functionalized carboxylate esters in which Nu is a $-NR^9R^{10}$ group.

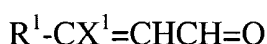
According to one embodiment of this aspect of the invention, the halogenated aliphatic- α,β -unsaturated- β -halocarboxylate ester may be part of an admixture that 25 also includes the corresponding dihalogenated aliphatic β,β -dihalocarboxylate ester that is not unsaturated at the α,β -position. Such a compound has the structure:



R^1 , X^1 and R^8 are the same as described above with respect to the halogenated aliphatic- α,β -unsaturated- β -halocarboxylate ester. X^2 is, independently of X^1 , F, Cl or Br. The α,β -saturated dihalocarboxylate ester dehydrohalogenates *in situ* to the halogenated aliphatic- α,β -unsaturated- β -halocarboxylate ester, which then reacts with the nucleophilic species to form the halogenated aliphatic- α,β -unsaturated- β -nucleophile-functionalized carboxylate ester.

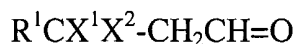
The halogenated aliphatic- α,β -unsaturated- β -halocarboxylate esters are prepared by esterification of the corresponding carboxylic acids. The β -halocarboxylate esters that are saturated at the α,β -position are likewise prepared by esterification of the corresponding carboxylic acids, and may then dehydrohalogenate *in situ* to the α,β -unsaturated- β -halocarboxylate esters.

According to one embodiment of this aspect of the invention, the halogenated aliphatic- α,β -unsaturated- β -halocarboxylic acids are formed by oxidation of aldehydes having the formula:



R^1 and X^1 are the same as described above for the halogenated aliphatic- α,β -unsaturated- β -halocarboxylate esters.

In a related embodiment, the halogenated aliphatic- β,β -dihalocarboxylic acids that are saturated at the α,β -position are formed by oxidation of aldehydes having the formula:



R^1 and X^1 are the same as described above for the α,β -unsaturated aldehydes and X^2 , independently of X^1 , is F, Cl or Br. The resulting α,β -saturated β,β -dihalocarboxylic

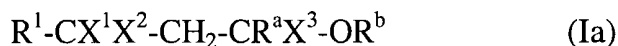
acids may then dehydrohalogenate to the corresponding α,β -unsaturated- β -halo-carboxylic acids.

According to another embodiment of this aspect of the present invention, the α,β -saturated and α,β -unsaturated aldehydes are together obtained by hydrolysis of a compound having the structure of Formula I:

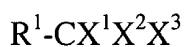


R^1 , X^1 and X^2 are the same as described above for the aldehydes. X^3 , independent of X^1 and X^2 , is Cl, Br or I. R^b is a straight chain or branched C_1 - C_6 alkyl.

According to another aspect of the present invention, a process is provided for the preparation of the compounds of Formula Ia (which include the compounds of Formula I):



The process includes the step of reacting a 1,1,1-trihalogenated aliphatic compound having the formula:



with an unsaturated compound having the formula:



using UV light or transition metal catalysis. R^a is hydrogen, a straight chain or branched C_1 - C_6 alkyl, a straight chain or branched C_1 - C_6 alkyl substituted with one or

more groups independently selected from halo, cyano, nitro, amido or nitrogen heterocycle containing five, six or seven ring members, a phenyl or a phenyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, C₁-C₆ alkyl or C₁-C₆ alkoxy. X¹, X², X³, R¹ and R^b are the same as described above with respect to Formula I.

The compounds of Formula I may also be hydrolyzed in the presence of a bisulfite salt to form useful intermediate, water-soluble compounds that may then be oxidized to the β-halocarboxylic acids of the present invention. Therefore, according to another aspect of the present invention, a process is provided including the step of hydrolyzing the compound of Formula I with a bisulfite salt having the formula M¹HSO₃, so that a mixture is obtained of a compound having the structure of Formula II:



and a compound having the structure of Formula III:



wherein R¹, X¹ and X² are the same as described above with respect to Formula I, Y is OH and Z is M¹SO₃, wherein M¹ is a cation selected from alkali metal cations, alkaline earth metal cations, NH₄⁺, NR²H₃⁺ and NR²R³H₂⁺, wherein R² and R³ are independently straight chain or branched C₁-C₆ alkyl, phenyl or phen C₁-C₆ alkyl. Oxidation of the bisulfite compounds of Formula II and Formula III to the corresponding carboxylic acids will include some dehydrohalogenation of the Formula II compounds to form the α,β-unsaturated-β-halocarboxylic acids.

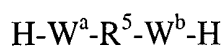
The compounds of Formula I may also be reacted with alcohols to form useful acetal intermediate compounds that may be then oxidized to the β -halocarboxylic acids of the present invention. Therefore, according to another aspect of the present invention, a process is provided including the step of reacting the compounds of

5 Formula I with alcohols having the formula R^4OH , so that a mixture is obtained of compounds having the structures of Formula II and Formula III, wherein R^1 , X^1 and X^2 are the same as described above with respect to Formula I, Y is OR^b or OR^4 , and Z is OR^4 , wherein R^4 is a straight chain or branched C_1 - C_6 alkyl, a straight chain or branched C_1 - C_6 alkyl substituted with one or more groups independently selected from halo, cyano, nitro, amido or nitrogen heterocycle containing 5, 6 or 7 ring members, a phenyl, or a phenyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, C_1 - C_6 alkyl or C_1 - C_6 alkoxy. Oxidation of the acetal compounds of Formula II and Formula III to the corresponding carboxylic acid derivatives will also include some dehydrohalogenation of the Formula II compounds

15 to form the α,β -unsaturated β -halocarboxylic acid derivatives.

The compounds of Formula I may also be reacted with diols, dithiols, diamines, aminoalcohols, aminothiols or thioalcohols to form useful cyclic intermediate compounds that may then be oxidized to the β -halocarboxylic acids of the present invention. Therefore, according to another aspect of the present invention,

20 a process is provided including the step of reacting the compound of Formula I with a compound having the Formula:



25 so that a mixture is obtained of compounds having the structures of Formula II and Formula III, wherein R^1 , X^1 and X^2 are the same as described above with respect to

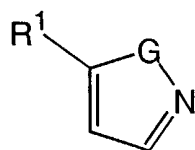
Formula I, and Y and Z together form a ring structure with the carbon to which they are attached having as members $-W^a-R^5-W^b-$, wherein W^a and W^b are independently selected from O, N and S, and R^5 is a C_2-C_3 alkylene optionally substituted with straight chain, branched or cyclic C_1-C_6 alkyl, or optionally forming part of 1,2-phenylene, which, in turn, is optionally ring-substituted with one or more groups selected from halo, cyano, nitro, amido, C_1-C_6 alkyl or C_1-C_6 alkoxy. Oxidation of the cyclic intermediate compounds of Formula II and Formula III to the corresponding carboxylic acid derivatives will include dehydrohalogenation of the Formula II compounds to form the α,β -unsaturated carboxylic acid derivatives.

The compounds of Formula I may also be reacted with a hydrazine to form useful hydrazone intermediate compounds that may then be oxidized to the β -halocarboxylic acids of the present invention. Therefore, according to another aspect of the present invention, a process is provided including the step of reacting the compounds of Formula I with a hydrazine having the formula NH_2NHR^6 , so that a mixture is obtained of compounds having the structures of Formula II and Formula III, wherein R^1 , X^1 and X^2 are the same as described above with respect to Formula I and Y and Z together form $=NNHR^6$ group, wherein R^6 is hydrogen, a straight chain or branched C_1-C_6 alkyl, a straight chain or branched C_1-C_6 alkyl substituted with one or more groups independently selected from halo, cyano, nitro, amido or nitrogen heterocycle containing 5, 6 or 7 ring members, a phenyl, or a phenyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, C_1-C_6 alkyl or C_1-C_6 alkoxy.

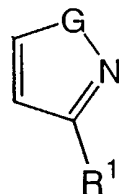
The compounds of Formula I may also be reacted with a hydroxylamine to form useful oxime intermediate compounds. Therefore, according to another aspect of the present invention, a process is provided including the step of reacting the compounds of Formula I with a hydroxylamine having the formula NH_2OR^7 , so that a

mixture is obtained of compounds having the structures of Formula II and Formula III, wherein R^1 , X^1 and X^2 are the same as described above with respect to Formula I and Y and Z together form $=NOR^7$ group, wherein R^7 is hydrogen, or a straight chain or branched C_1-C_6 alkyl.

5 The oxime and hydrazone compounds of Formula II and Formula III may be further reacted by heating with or without acid or base catalysis to form useful heterocyclic compounds. Therefore, according to another embodiment of this aspect of the invention the methods of forming the hydrazone and oxime compounds of the present invention further include the steps of further heating the hydrazone and oxime compounds so that heterocyclic compounds are obtained having the structures of Formula IVa and Formula IVb:



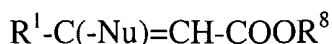
IVa



IVb

wherein G is O or NR^6 , R^1 is the same as described above with respect to Formula I, and R^6 is the same as described above with respect to the hydrazone compounds of Formula II and Formula III.

15 The processes of the present invention prepare useful compounds having biological and pharmaceutical activity, and intermediate compounds useful in the preparation of compounds having biological and pharmaceutical activity. Therefore, according to another aspect of the present invention, halogenated aliphatic- α,β -unsaturated- β -nucleophile-functionalized carbocyclic acids and derivatives thereof are
20 provided having the formula:

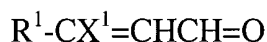


wherein R^1 is selected from straight chain and branched halogenated C_1-C_{12} aliphatic groups;

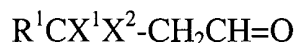
5 Nu is a nucleophile moiety; and

R^8 is selected from hydrogen, straight chain and branched C_1-C_6 alkyl groups, NH_4^+ , $R^2NH_3^+$, alkali metal ions, alkaline earth metal ions, Cl, NH_2 , NHR^2 , $NHNHR^2$, CN, SH and SR^2 , wherein R^2 is selected from straight chain or branched C_1-C_6 alkyl, phenyl or phen C_1-C_6 alkyl.

According to another embodiment of this aspect of the invention, aldehyde compounds are provided having the formulae:



15 and:



wherein R^1 , X^1 and X^2 are as described above for the aldehydes. According to another embodiment of this aspect of the invention, compounds are provided having the structures of Formula I and Formula Ia, wherein R^1 , X^1 , X^2 , X^3 , R^a and R^b are as described above for these compounds.

According to yet another embodiment of this aspect of the invention, compounds are provided having the structures of Formula II and Formula III, wherein R^1 , X^1 and X^2 are the same as described above for these compounds, and Y and Z are selected so that Y is OH when Z is M^1SO_3 , Y is OR^1 when Z is OR^4 , or Y and Z together form a $=NNHR^6$ group, a $=NHOR^7$ group or, a ring structure with the carbon

to which they are attached having as members $-W^a-R^5-W^b-$, wherein M^1 , R^1 , R^4 , R^5 , R^6 , R^7 , W^a , and W^b are the same as described above for Formula II and Formula III.

According to still yet another embodiment of this aspect of the invention, heterocyclic ring compounds are provided having the structures of Formula IVa and Formula IVb, wherein G , R^1 and R^6 are the same as described above for Formula IVa and Formula IVb.

As is more specifically shown in Step 1 of the five step inventive process, a halofluorocarbon is catalytically added to a substituted vinyl ether to obtain the compound of Formula Ia:



using UV light catalysis or transition metal catalysis, wherein R^a is hydrogen, or straight chain or branched C_1 - C_6 alkyl, or straight chain or branched C_1 - C_6 alkyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, or nitrogen heterocycle containing five, six or seven ring members; or phenyl, or phenyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy; R^b is straight chain or branched C_1 - C_6 alkyl; X^1 and X^2 are independently selected from F, Cl and Br; X^3 , independently of X^1 and X^2 is Br, Cl or I; and R^1 is a straight chain or branched halogenated C_1 - C_{12} aliphatic group. R^a is preferably hydrogen, in which case the compounds of Formula Ia are the compounds of Formula I. R^1 is preferably polyhalogenated, and is most preferably polyfluorinated or perfluorinated.

Step 1.



The inventive process generates useful intermediate compounds. Fluoroalkyl intermediate compounds are provided that are precursors to bioactive compounds, and others that are (or of themselves may be) bioactive, and thus are of commercial value in pharmaceutical and agricultural applications.

5 In Step 2 of the inventive process, C-1 of Formula I, the carbon bearing the halogen X^3 and the $-OR^b$ group, is modified by one of two general methods of broad utility:

The hydrolysis of compounds of Formula I is accomplished as outlined in Step 2a to form the intermediate aldehydes $R^1-CX^1X^2CH_2CH=O$ and $R^1-CX^1=CHCH=O$ in water, or more preferably in a mixture of water and an organic solvent, e.g., acetone, tetrahydrofuran, or 1,2-dimethoxyethane. R^1 , X^1 and X^2 are the same as described above with respect to Formula I.

Step 2a.



Novel variations of the hydrolysis induce derivitization of C-1 of Formula I, as indicated in Step 2b. When a compound of Formula I is hydrolyzed in the presence of an organic solvent and a bisulfite salt, M^1HSO_3 , there is produced the novel intermediate compounds of Formula II and Formula III:

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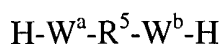


wherein R^1 , X^1 and X^2 are the same as described above with respect to Formula I, Y is $-OH$ and Z is $-SO_3M^1$.

These novel intermediate compounds can be used in organic or in water solution, they can be isolated as stable solids, and they can be converted to the corresponding aldehydes in aqueous acid or base. Furthermore, these sulfonic acid salts chemically behave in a manner similar to the aldehydes without the need to isolate the aldehyde, and offer certain process advantages such as enhanced water solubility, improved stability and materials handling. The ion M^1 includes ammonium ion, NH_4^+ , alkylammonium ions, $NR^2H_3^+$, and $NR^2R^3H_2^+$, (where R^2 and R^3 are independently a straight chain or branched C_1 - C_6 alkyl, phenyl or phen C_1 - C_6 alkyl), alkali metal ions, e.g., Na^+ , and K^+ , and alkaline earth metal ions e.g., Ca^{+2} , and Ba^{+2} .

When the compounds of Formula I are reacted with an alcohol, R^4OH , there are produced acetal intermediate compounds having the structures of Formula II or Formula III wherein Y is OR^b or OR^4 and Z is OR^4 . R^4 is straight chain or branched C_1 - C_6 alkyl, or straight chain or branched C_1 - C_6 alkyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, or nitrogen heterocycle containing five, six or seven ring members; or phenyl, or phenyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy.

When the structures of Formula I are reacted with a 1,2-diol, a 1,3-diol, a 1,2-diothiol, a 1,3-diothiol, a 1,2-diamine, a 1,3-diamine, a β -aminoalcohol, a γ -aminoalcohol, a β -aminothiols, or a γ -aminothiols, i.e. compounds having the structure:



there are produced the novel cyclic intermediate compounds having the structures of Formula II or Formula III wherein Y and Z together with the carbon to which they are

attached form a ring having as members $-W^a-R^5-W^b-$, wherein W^a , and W^b are independently selected from O, N or S. R^5 is a C_2-C_3 alkylene optionally substituted with straight chain, branched or cyclic C_1-C_6 alkyl, or a C_2-C_3 alkylene that is part of a 1,2-phenylene, or a C_2-C_3 alkylene that is part of a 1,2-phenylene substituted with one or more groups selected from halo, cyano, nitro, amido, C_1-C_6 alkyl or C_1-C_6 alkoxy. These novel intermediates can be used in solution, they can be isolated, and they can be converted to the corresponding aldehyde in aqueous acid or with an aqueous Lewis acid, e.g., BF_3 .

When the compounds of Formula I are reacted in an organic solvent, e.g., acetic acid, with a hydrazine, NH_2NHR^6 there is produced the novel hydrazone intermediate compounds having the structures of Formula II or Formula III wherein Y and Z together form an $=NNHR^6$ group, wherein R^6 is hydrogen, or straight chain, branched or cyclic C_1-C_6 alkyl, or straight chain, branched or cyclic C_1-C_6 alkyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, or nitrogen heterocycle containing five, six or seven ring members; or phenyl, or phenyl substituted with one or more groups independently selected from halo, cyano, nitro, amido, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or C_1-C_6 alkanesulfonyl, or phenylsulfonyl, or phenylsulfonyl substituted with C_1-C_6 alkyl.

When the compounds of Formula I are reacted in an organic solvent, e.g., methanol, with a hydroxylamine, NH_2OR^7 , there is produced the novel oxime intermediate compounds having the structures of Formula II or Formula III, wherein Y and Z together form a $=NOR^7$ group, wherein R^7 is hydrogen, or C_1-C_6 alkyl. These novel intermediate compounds can be used in solution, they can be isolated, and they can be converted to the corresponding aldehyde in aqueous acid.

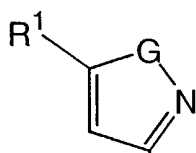
Step 2b.

Formula I + Reagent $\rightarrow$ $R^1-CX^1X^2CH_2CHYZ$ (Formula II) +

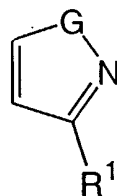
$R^1-CX^1=CH-CHYZ$ (Formula III)

R^1 , X^1 and X^2 are the same as described above with respect to Formula I, the reagent is an alcohol, 1,2-diol, 1,3-diol, 1,2-thiol, 1,3-thiol, 1,2-diamine, 1,3-diamine, β -aminoalcohol, γ -aminoalcohol, β -aminothiols, γ -aminothiols, hydrazine, hydroxylamine, and the like, and Y and Z correspond to the groups above-described as being obtained when these reagents are used.

The oxime and hydrazone derivatives can be further heated to produce the heterocyclic derivatives of Formula IV, wherein G is O or NR^6 wherein R^6 is defined as before, and R^1 is the same as described above with respect to Formula I



IVa



IVb

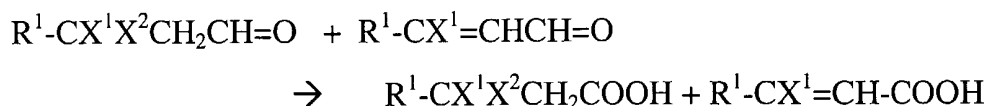
It is understood that dehydrohalogenation to halogenated- α,β -unsaturated- β -halocarboxaldehydes, $R^1-CX^1=CH-CH=O$, and to the various halogenated- α,β -unsaturated- β -haloalkane structures of Formula III, $R^1-CX^1=CH-CHYZ$, can occur to varying amounts depending on the specific reaction and process conditions in Steps 2a, and 2b.

In Step 3a and Step 3b the aldehydes from Step 2a or the related derivatives from Step 2b respectively are oxidized to the intermediates $R^1-CX^1X^2CH_2COOH$ and

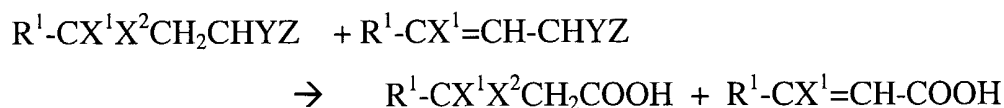
$R^1-CX^1=CH-COOH$ using e.g., chromic acid, potassium permanganate, or other oxidizing agents known to those skilled in the art. R^1 , X^1 and X^2 are the same as described above with respect to Formula I.

Step 3a.

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Step 3b.



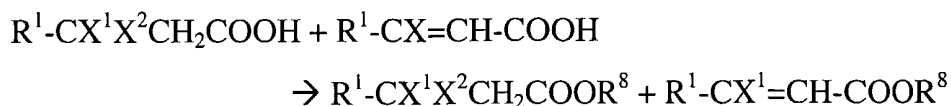
It is understood that dehydrohalogenation to halogenated- α,β -unsaturated- β -halocarboxylic acids, $R^1-CX^1=CH-COOH$, can occur to varying amounts depending on the specific oxidizing agent and reaction conditions in Step 3a and 3b. The carboxylic acids from Step 3a and 3b can be isolated as salts $R^1-CX^1X^2CH_2COOM^2$ and $R^1-CX^1=CH-COOM^2$, where the ion M^2 includes ammonium ion, NH_4^+ , alkylammonium ion, $R^2NH_3^+$, alkali metal ions, e.g., Na^+ , and K^+ , and alkaline earth metal ions e.g., Ca^{+2} , and Ba^{+2} . It is further recognized that the carboxylic acid, -COOH, can be reacted to form standard derivatives such as -CO-Cl, -CO-NH₂, -CO-NHR, -CO-NHNHR, -CN, -CO-SH, and -CO-SR by standard methods known to those skilled in the art.

Step 4 involves the esterification of the carboxylic acid derivatives from Step 3a and 3b with a compound capable of transferring the alkyl group, R^8 , to obtain the alkyl ester thereof. The reaction can be carried out in the presence of a base, e.g., potassium carbonate, with an alkylating agent, e.g., an alkyl halide such as ethyl

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bromide. The reaction can be carried out in the presence of an acid, e.g., methanesulfonic acid, and excess alcohol, e.g., n-butanol. R^8 is a straight chain or branched C_1 - C_6 alkyl.

5 Step 4.



It is understood that dehydrohalogenation to halogenated- α,β -unsaturated- β -halocarboxylate esters, $R^1-CX^1=CH-COOR^8$, can occur to varying amounts depending on the specific reaction conditions in Step 4.

The final product, having the structure of Formula V:

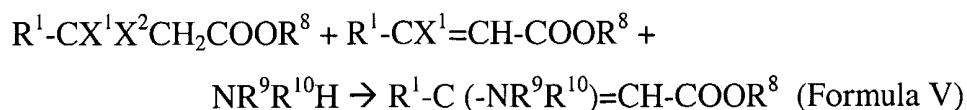


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is obtained in Step 5a, by reaction of $R^1-CX^1X^2CH_2COOR^8$ and $R^1-CX^1=CH-COOR^8$ with a reagent capable of transferring a substituted-amino group.

Step 5a.

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It is understood that structures $R^1-CX^1X^2CH_2COOR^8$ undergo dehydrohalogenation *in situ* to halogenated- α,β -unsaturated- β -halocarboxylate esters, which then react further to form the desired $R^1-C(-NR^9R^{10})=CH-COOR^8$. R^9 and R^{10} are independently selected from hydrogen, and straight chain or branched C_1 - C_6 alkyl.

In Step 5b, in a similar manner, other nucleophilic species, Nu, react with the esters from Step 4 to produce a halogenated- α,β -unsaturated- β -(Nu-functionalized) carboxylate ester of Formula VI:

5 Step 5b.



Nu is selected from anionic species, for example halide ion, I^- , Br^- , F^- , or alkoxide ion, phenoxide ion, or substituted-phenoxide ion, alkylamide ion, thiolate ion, acyloxy anion, cyanide ion, azide ion, cyanate ion, thiocyanate ion, or neutral species, for example straight chain or branched or cyclic C_1 - C_6 alkyl alcohols, or alkyl or aryl thiols.

Steps 1-5 occur at or near atmospheric pressure. The temperature of reaction ranges from 0 °C to 100 °C. The method of separating the intermediates and the final products from the reaction mixtures are selected from standard manipulative techniques, including distillation, or crystallization.

Another aspect of the present invention is that the compounds of Formula V and VI wherein R^1 is CF_3 are chemically equivalent and convertible to trifluoromethyl ketone derivatives, $CF_3-CO-CH=CH-COOR^8$. Such ketones have been used as intermediates in heterocyclic synthesis and have also been viewed as synthetic targets because of their possible pharmacological interest. Trifluoromethyl ketones are a particularly well-documented class of serine protease inhibitors, which have proven attractive against elastase, chymotrypsin, and CMV protease.

By way of further description of the various substituents in the inventive process R^1 as a halogenated aliphatic radical, is preferably a substituted or unsubstituted C_1 - C_{12} halogenated aliphatic radical, and is more preferably fluorinated. Even more preferably, R^1 is a perfluorinated aliphatic radical, and more preferably

perfluorinated. Examples of substitution groups include C₁-C₆ aliphatics such as alkyls, alkyl ethers, alkyl esters and alkenyls containing nitro, aminos (primary and secondary), cyano, hydroxyl, thiol and alkylthio groups. The substitution groups are preferably attached to non-fluorinated carbon atoms of R¹.

5 R¹ as a C₁-C₁₂ halogenated alkyl radical may be straight-chained or branched, for example, halogenated methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, n-heptyl, n-octyl or 2-ethylhexyl. Any of these groups may be substituted with essentially any conventional organic moiety, for example, methoxy, ethoxy, n- or iso- propoxy, n-butoxy, methane sulphonyl or cyano.

C₁-C₆ fluorinated alkyl radicals are even more preferred. Examples include fluoromethyl, difluoromethyl, trifluoromethyl, fluorethyl, difluoroethyl, trifluoroethyl, pentafluoroethyl, perfluoropropyl, perfluorobutyl, perfluoropentyl or perfluorohexyl. In the most preferred form, R¹ is a trifluoromethyl radical.

15 Two preferred halofluorocarbon starting materials are the isomeric pair CFC-113 (1,2,2-trichloro-1,1,2-trifluoroethane) and CFC 113a (1,1,1-trichloro-2,2,2-trifluoroethane). More preferably, the starting material is 1,1,1-trichloro-2,2,2-trifluoroethane, CFC-113a, which has the structure of CF₃CCl₃. It has been discovered that CFC-113a reacts with specificity in a way that allows incorporation of the CF₃- functional group into the target molecules.

20 In Step 1 of the present invention the halofluorocarbon is photocatalytically added to an alkyl vinyl ether, preferably at a temperature between 25-40 °C. Suitable reagents, solvents and process conditions may be determined by reference to Bosone et.al., Pesticide Sci., 17(6), 621-630 (1986) and also to EP 31,041, both incorporated herein by reference. Conditions suitable for transition metal catalyzed addition of
25 halofluorocarbons to trialkylsilyl vinyl ethers may be determined by reference to Eguchi et al., J. Org. Chem., 58, 5163-5166 (1993) incorporated herein by reference.

The hydrolysis of Step 2a is carried out over a period of 2-12 hours at approximately 20 °C, preferably with aqueous tetrahydrofuran, followed by isolation of the aldehyde, or by further reaction with one of the reagents of Step 2b. In a preferred example of derivatization in Step 2b, structures of Formula I are stirred with a solution of NaHSO₃ in aqueous tetrahydrofuran for 5-20 hours at 20 °C, and the majority of the water and tetrahydrofuran are removed in vacuo, and the solid halogenated hydroxyalkanesulfonic acid salt is isolated by filtration.

The oxidation of Step 3 is performed in aqueous chromic acid for 15-25 hours at approximately 20 °C in the presence of an organic solvent, for example diethyl ether, or dibutyl ether, or more preferably tetrahydrofuran, followed by phase separation, washing with brine and vacuum distillation. The oxidation of Step 3 may also be performed using hypochlorous acid in alcohol solvent to allow direct formation of the corresponding carboxylate ester.

The esterification of Step 4 is best performed in the presence of excess alcohol, for example methanol, ethanol or n-butanol, and an acid catalyst, for example methanesulfonic acid with sufficient heat to cause reaction. The water produced is distilled off as an azeotrope with the alcohol, or is removed by trapping with the appropriate drying agent, e.g., 3A molecular sieve. The ester is then isolated by direct distillation from the reactor.

The reaction of the ester with the substituted amine in Step 5 preferably involves stirring the haloester with an excess of the substituted-amine in water solvent or in an organic solvent, or more preferably neat, at approximately 0-75 °C, at a pressure of approximately 0-200 psig for 1-20 hours. Following the reaction, the amine hydrochloride salt solid by-product is filtered off or is extracted from the mixture with water and the desired halogenated-β- (substituted-amino) crotonate ester is distilled or recrystallized.

Example 1. Ethyl 3-methylamino-4, 4,4-trifluorocrotonate (Step 5a)

Ethyl 3-chloro-4,4,4-trifluorocrotonate (2.01 g, 9.93 mmol) was placed in a 90 cc glass pressure reactor containing a magnetic stir bar. The system was freeze-thaw degassed and then anhydrous methylamine (5 g) was condensed into the reactor at
5 -70 °C. The mixture was warmed to 15-20 °C with stirring for 90 minutes. Excess methylamine was vented; the methylamine hydrochloride solid was filtered off, and rinsed with 1 mL of CH₂Cl₂. The filtrate was distilled to yield 1.5 g of ethyl 3-methylamino-4,4,4-trifluorocrotonate, bp 70 °C at ca. 20 mm Hg.

Example 2. Ethyl 3-Cyano-4,4,4-trifluorocrotonate by Reaction of Ethyl 3-chloro-4,4,4-trifluorocrotonate with Potassium Cyanide (Step 5b)

A mixture of ethyl 3-chloro-4,4,4-trifluorocrotonate (4.0 g, 20 mmol) and potassium cyanide (1.4 g, 21 mmol) in 25 mL of ethanol was refluxed under nitrogen for 10 hours. The mixture was fractionally distilled to provide the ethyl 3-cyano-4,4,4-
15 trifluorocrotonate in 85 % yield.

Example 3. 3,3-Dichloro-4,4,4-trifluorobutyraldehyde and 3-Chloro-4,4,4-trifluorocrotonaldehyde (Step 2a)

n-Butyl 1,3,3 trichloro-4,4,4-trifluorobutyl ether was added to a stirred mixture of
20 excess water and tetrahydrofuran at 25 °C, with additional stirring for 2 hours. GC and NMR analyses indicated > 99 % conversion with > 99 % selectivity for 3,3-dichloro-4,4,4-trifluorobutyraldehyde. The addition of aqueous potassium hydroxide to pH-adjust to pH +1.0 causes dehydrochlorination to 3-chloro-4,4,4-trifluorocrotonaldehyde in >95% conversion and >75% selectivity by gc and nmr analyses.

Comparative Example 1. Preparation of 3,3-Dichloro-4,4,4-trifluorobutyraldehyde in Aqueous Sodium Carbonate

n-Butyl 1,3,3-trichloro-4,4,4-trifluorobutyl ether (287.8 g, 1.0 mol) was stirred with 1.12L of 10 % (wt) aqueous sodium carbonate for 24 hours under nitrogen. The insoluble organic layer was phase separated, dried over MgSO₄, and distilled to provide 58.1 g of 3-chloro-4,4,4-trifluorocrotonaldehyde (32% yield), ca. 88 % pure by GC and NMR analyses, bp 74-78 °C, as a bright yellow lachrymatory oil, and 4 g of 3,3-dichloro-4,4,4-trifluorobutyraldehyde, (3% yield), bp ca 85-95 °C.

Example 4. 3,3-Dichloro-1-hydroxy-4,4,4-trifluorobutanesulfonic Acid Sodium Salt (Step 2b)

n-Butyl 1,3,3 trichloro-4,4,4-trifluorobutyl ether (28.74 g, 0.1 mol) was added to a stirred mixture of tetrahydrofuran (88.4 g) and 59.7 g of an aqueous solution of 40%(wt) sodium bisulfite, with additional stirring for 12 hours. NMR analyses indicated > 99 % conversion with >99 % selectivity for 3,3-dichloro-4,4,4-trifluoro-1-hydroxybutanesulfonic acid sodium salt. The volatiles were removed in vacuo to leave 38.6 g of solid containing of crude 3,3-dichloro-1-hydroxy-4,4,4-trifluorobutanesulfonic acid sodium salt as a stable white salt.

Example 5. 3,3-Dichloro-1-hydroxy-4,4,4-trifluorobutanesulfonic Acid Sodium Salt, and 3-Chloro-1-hydroxy-4,4,4-trifluoro-2-butenesulfonic Acid Sodium Salt (Step 2b)

n-Butyl 1,3,3 trichloro-4,4,4-trifluorobutyl ether (29.57g, 0.10 mol) was added dropwise to a mixture of tetrahydrofuran (100 mL) and saturated aqueous brine (29 mL) maintained at 25 °C. After 30 minutes the organic layer is separated and washed with brine. The organic layer is then added to 48.9 g of 40 % (wt) sodium bisulfite

solution at 25 °C with stirring for an additional 20 hours. The organic layer (upper) is phase separated and stripped to dryness in vacuo to yield 26.46 g of stable white solid crystals. NMR analyses indicated > 99 % conversion to a mixture of 3,3-dichloro-4,4,4-trifluoro-1-hydroxybutane-sulfonic acid sodium salt (92 %) and 3-chloro-4,4,4-trifluoro-1-hydroxy-2-butene-sulfonic acid sodium salt (8 %).

Example 6. Preparation of the Hydrazone of 3-Chloro-4,4,4-trifluorocrotonaldehyde (Step 2b)

To a solution of n-butyl 1,3,3-trichloro-4,4,4-trifluorobutyl ether (4.32 g, 15 mmol), acetic acid (10.4 g, 0.17 mol), water (3.25 g), and *p*-toluenesulfonic acid monohydrate (0.58 g) was added at once hydrazine monohydrate (6.03 g, 0.12 mol) with vigorous stirring under nitrogen, and with external cooling to maintain the temperature below 60 °C. After 1 hour the reaction mixture was analyzed by GC, GC/MS, and ¹⁹F and ¹H NMR and found to contain a trace of unreacted starting material, and 3-(trifluoromethyl) pyrazole (17%), plus a component identified as the hydrazone of 3-chloro-4,4,4-trifluorocrotonaldehyde (69%).

Example 7. 3-Chloro-(1,1-ethylenedioxy)-4,4,4-trifluoro-2-butene (Step 2b)

n-Butyl 1,3,3-trichloro-4,4,4-trifluorobutyl ether (286.4 g, 1.0 mol) was slowly added to stirred ethylene glycol (389 g, 6.3 mol) at 105 °C (Note exotherm) with additional stirring for 2-3 hours at 105 °C until HCl gas evolution ceased. The reaction mixture was fractionally distilled to yield 97.3 g of 3-chloro-(1,1-ethylenedioxy)-4,4,4-trifluoro-2-butene, bp 71-85 °C at 30 mm Hg.

Example 8. 3-Chloro-((1,1),(3,3)-bis-ethylenedioxy)-4,4,4-trifluorobutane

Examination of the pot residue, 50.1 g of a mobile red oil from Example 7 indicated the major component to be 3-chloro-((1,1),(3,3)-bis-ethylenedioxy)-4,4,4-trifluorobutane, identified by NMR and GC/MS.

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Example 9. 3-Chloro-4,4,4-trifluorocrotonic Acid, and 3,3-Dichloro-4,4,4-trifluorobutyric Acid (Step 3a)

Dilute aqueous chromic acid (540 g, ca. 0.9 mol) was added over 1 hour to a stirred solution of 3-chloro-4,4,4-trifluorocrotonaldehyde and 3,3-dichloro-4,4,4-trifluorobutyraldehyde (71.3 g total, ca 0.4 mol) in diethyl ether (700 ml) at 20 °C. After stirring 18 hours at 20 °C the mixture was phase separated and the organic phase was washed with brine. Distillation gave 69.2 g of a mixture of 3-chloro-4,4,4-trifluorocrotonic acid (major), and 3,3-dichloro-4,4,4-trifluorobutyric acid (minor), bp 65-75 °C at 4 mm Hg as oily colorless crystals, 95 % pure by GC and by NMR analyses.

15

Example 10. 3-Chloro-4,4,4-trifluorocrotonic Acid and 3,3-Dichloro-4,4,4-trifluorobutyric Acid (Step 3b)

Dilute aqueous chromic acid (18 g) was added over 1 hour to a stirred mixture of 1.04 g of the sulfonic acid salts from Example 5 in water (3.1 g) and ether (3.2 g) at 20 °C. After stirring 18 hours at 20 °C the mixture was phase separated and the organic phase was washed with brine. NMR and GC analyses indicated a mixture of 3,3-dichloro-4,4,4-trifluorobutyric acid and 3-chloro-4,4,4-trifluorocrotonic acid in > 90% purity.

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Example 11. Ethyl 3-chloro-4,4,4-trifluorocrotonate (Step 4)

A solution of 3-chloro-4,4,4-trifluorocrotonic acid (2.0 g) was stirred with a solution of methanesulfonic acid (0.05 g) in ethanol at reflux for 6 hours under nitrogen with slow removal of the distillate containing water of reaction. The reaction mixture was then fractionally distilled in vacuo to give 1.8 g of ethyl 3-chloro-4,4,4-trifluorocrotonate, bp 82-83 °C at 108 mm Hg, > 95 % pure by GC and NMR.

Example 12. Preparation of 3-(Trifluoromethyl)pyrazole (Step 2b)

To a solution of p-toluenesulfonic acid monohydrate (46 g, 0.24 mol) in anhydrous acetic acid (432 g, 7.2 mol) was added hydrazine monohydrate (185 g, 3.62 mol) with vigorous stirring over 10 mins under nitrogen and external cooling to maintain the temperature below 100 °C. Crude butyl 1,3,3-trichloro-4,4,4-trifluorobutyl ether (345 g, 1.2 mol) was added over 25 mins with vigorous stirring at 95 °C. An exotherm ensues within 3 mins of complete addition causing vigorous reflux at 107 °C, accompanied by rapid HCl gas evolution (Caution, this is an extremely vigorous reaction!). A suspension (hydrazine hydrochloride salt) formed. Stirring continued at 85-100 °C for another 75 mins. Butyl acetate and acetic acid were distilled off, at 60°C and 70-15 mm Hg to constant weight, ca. 470 g. The semi-solid was cooled to 20 °C, followed by the addition of 500 mL hexane. After cooling to 10 °C 720 mL of 10 % (wt) aqueous sodium carbonate was added over one hour with vigorous stirring under nitrogen. Solid sodium bicarbonate (175 g) was then added incrementally over 2 hours at 10 °C; stirring continued for an additional hour until there was no further CO₂ gas evolution. The solids were filtered off, with the filter cake rinsed with hexane (two times with 150 mL). The combined organic layers were washed with 200 mL of saturated brine solution and then distilled through a 6" vigreux column to

provide 108.2 g (66% yield) 3-(trifluoromethyl) pyrazole as a white-cream colored solid, bp 63 °C at 2 mm Hg, mp 46-50 °C, > 97 % pure (GC, and ¹H and ¹⁹F NMR).

Comparative Example 2. Attempted Preparation of 3-(Trifluoromethyl)

5 **Pyrazole: Sodium Dithionite Procedure**

The literature procedure was conducted without success (see C-M. Hu et al., J. Chem. Soc., Perkins Transactions I, 2161-2163 (1994)).

**Comparative Example 3. Attempted Preparation of 3-(Trifluoromethyl)
pyrazole: Reaction of Hydrazine Hydrate with n-Butyl 1,3,3-Trichloro-4,4,4-
trifluorobutyl Ether in Refluxing Ethanol; Preparation of 1-n-Butoxy -3,3-
Dichloro-1-Ethoxy-4,4,4-trifluorobutane**

15 A solution of n-butyl 1,3,3-trichloro-4,4,4-trifluorobutyl ether (1.47 g, 5.1 mmol), hydrazine monohydrate (1.99 g, 24.9 mmol) and ethanol (11 mL) was refluxed under nitrogen for four hours. GC indicated a single new component, and ¹H and ¹⁹F NMR were consistent with formation of the mixed acetal 1-n-butoxy-3,3-dichloro-1-ethoxy-4,4,4-trifluorobutane.

Comparative Example 4. Attempted Preparation of 3-(Trifluoromethyl)

20 **pyrazole: Reaction of Hydrazine Hydrate with n-Butyl 1,3,3-Trichloro-4,4,4-
trifluorobutyl Ether at 85 °C in Ethanol Containing Aqueous Acetic Acid**

25 A solution of butyl 1,3,3-trichloro-4,4,4-trifluorobutyl ether (1.44 g, 5.0 mmol), hydrazine monohydrate (2.0 g, 25 mmol), acetic acid (1.5 g, 26 mmol), water (1.0 g, 58 mmol), p-toluenesulfonic acid monohydrate (0.05 g, 0.2 mmol) and ethanol (10 mL) was stirred at 85 °C under nitrogen for 2 hours. GC indicated a single

component, and ^1H and ^{19}F NMR were consistent with formation of the mixed acetal 1-n-butoxy-3,3-dichloro-1-ethoxy -4,4,4-trifluorobutane.

Example 13. Ethyl 3-amino-4,4,4-trifluorocrotonate by Reaction of Ethyl 3-chloro-4,4,4-trifluorocrotonate with Anhydrous Ammonia (Step 5a)

Ethyl 3-chloro-4,4,4-trifluorocrotonate (2.01 g, 9.93 mmol) was placed in a 90 cc glass pressure reactor containing a magnetic stir bar. The system was freeze-thaw degassed and then anhydrous ammonia (5.03 g, 295 mmol) was condensed into the reactor at -70°C . The mixture was warmed to $15\text{--}20^\circ\text{C}$ with stirring for 90 minutes (P_{max} ca. 102 psig.). Excess ammonia was vented, the NH_4Cl solid was filtered off, and rinsed with 1 mL of CH_2Cl_2 to give 0.45 g white solid NH_4Cl (92 %). The filtrate was distilled to yield 1.76 g of ethyl 3-amino-4,4,4-trifluorocrotonate (97% yield), bp 71°C at 27 mm Hg, colorless oily solid, mp ca. 20°C .

Example 14. Ethyl 3-amino-4,4,4-trifluorocrotonate by Reaction of Ethyl 3-chloro-4,4,4-trifluorocrotonate with Aqueous Ammonia (Step 5a)

Ethyl 3-chloro-4,4,4-trifluorocrotonate (ca. 50 mg, mmol) was stirred with 0.5 mL of 29 % (wt) aqueous ammonia at 25°C for 2 hours. The clear colorless solution was extracted with 0.2 mL methylene chloride. GC analysis indicated $> 99\%$ conversion with 100 % selectivity for ethyl 3-amino-4,4,4-trifluorocrotonate.

Example 15. Ethyl 3-amino-4,4,4-trifluorocrotonate by Reaction of Ethyl 3-chloro-4,4,4-trifluorocrotonate with Ammonium Acetate (Step 5a)

A solution of ethyl 3-chloro-4,4,4-trifluorocrotonate (0.99 g, 4.89 mmol) and ammonium acetate (7.70 g, 100 mmol) in 12 mL of ethanol was refluxed under nitrogen with periodic GC analysis; see Table 1 for results.

Table 1. Formation of Ethyl 3-amino-4,4,4-trifluorocrotonate Using Ammonium Acetate in Refluxing Ethanol (Relative GC area %)

Hours of reflux	$\text{CF}_3\text{-CCl}=\text{CH-COO-C}_2\text{H}_5$	$\text{CF}_3\text{-C(NH}_2)=\text{CH-COO-C}_2\text{H}_5$
0	100	0
2	41	59
7.5	22	78
26.5	12	88
28.5 *	9	91

* Note: an additional 1.54 g (20 mmol) of ammonium acetate was added after 26 hours of reflux.

5

Example 16. n-Butyl 1,3,3-Trichloro-4,4,4-trifluorobutyl Ether (Step 1)

A solution of CF_3CCl_3 (1438 g, 7.67 mol) and *n*-butyl vinyl ether (254 g, 2.49 mol) was irradiated with a 450 watt medium pressure Hg UV lamp with quartz immersion well for 2.5 hours with stirring at 40°C. Conversion is 100% and the majority of the excess CF_3CCl_3 was distilled off in vacuo leaving a residual clear light yellow-colorless oil containing 88% (mol) *n*-butyl 1,3,3 trichloro-4,4,4-trifluorobutyl ether and 12% CF_3CCl_3 . The yield of ether is 700g (98 % yield), > 98 % pure (excluding 113a, by ^1H and ^{19}F NMR analysis.) The ether, stable when stored under nitrogen at 5°C, is used without further purification.

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Example 17. Ethyl 1,3,3-trichloro-4,4,4-trifluorobutyl Ether (Step 1)

A solution of CF_3CCl_3 (850 g, 4.53 mol) and ethyl vinyl ether (218 g, 3.03 mol) was irradiated similarly to Example 16 above. After 12 hours the conversion and

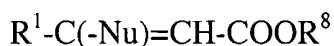
selectivity is > 90%. The majority of the excess CF₃CCl₃ was distilled off in vacuo leaving a clear light yellow – colorless oil in 70-90 % yield by nmr analysis. This ethyl ether derivative is unstable, and is used immediately without further purification.

5 **Example 18. Ethyl 3-chloro-4,4,4-trifluorocrotonate (Step 4)**

A solution of 3-chloro-4,4,4-trifluorocrotonic acid (15.6 g, 0.090 mol) was stirred with a mixture of anhydrous potassium carbonate (14.1 g, 0.102 mol), ethyl bromide (221 g, 2.03 mol), Aliquat 336TM (0.5 h, 1.3 mmol), and Adogen 464TM (0.57 g) at 25 °C for 93 hours under nitrogen. Then inorganic solids were filtered off through a thin pad of silica gel with rinsing by methylene chloride. Distillation gave 10.3 g (57 % yield) of ethyl 3-chloro-4,4,4-trifluorocrotonate, bp 82-83°C at 108 mm Hg, > 99 % pure by GC and NMR.

CLAIMS

1. A process for preparing a halogenated aliphatic- α,β -unsaturated- β -nucleophile-functionalized carboxylate ester having the formula:



comprising reacting a nucleophile with a halogenated aliphatic- α,β -unsaturated- β -halocarboxylate ester having the formula:



wherein R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups;

Nu is a nucleophile moiety different from X^1 ;

X^1 is F, Cl or Br; and

R^8 is selected from the group consisting of straight chain and branched C_1 - C_6 alkyl groups.

2. The process of claim 1, wherein said nucleophile is selected from the group consisting of F^- , Cl^- , Br^- , I^- , alkoxide ions, phenoxide ions, substituted phenoxide ions, alkylamide ions, thiolate ions, acyloxy ions, cyanide ions, azide ions, cyanate ions, thiocyanate ions, straight chain, branched and cyclic C_1 - C_6 alkyl alcohols, straight chain, branched and cyclic C_1 - C_6 alkyl thiols and arylthiols.

3. The process of claim 1, wherein said nucleophile is an amine compound having the formula $\text{NR}^9\text{R}^{10}\text{H}$, wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen and straight chain and branched $\text{C}_1\text{-C}_6$ alkyl groups.

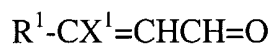
5 4. The process of claim 1, wherein said halogenated aliphatic- α,β -unsaturated- β -halocarboxylate ester is in admixture with a halogenated aliphatic- α,β -saturated- β,β -dihalocarboxylate ester having the formula:



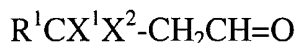
wherein X^2 is, independently of X^1 , F, Cl or Br.

5. The process of claim 4, wherein said halogenated aliphatic- β -halocarboxylate esters and halogenated aliphatic- α,β -saturated- β,β -dihalocarboxylate
15 esters are prepared by esterification of carboxylic acids.

6. The process of claim 5, wherein the halogenated aliphatic- β -halocarboxylic acids and halogenated aliphatic- α,β -saturated- β,β -dihalocarboxylic acids are formed by oxidation of an admixture of aldehydes having the formulae:

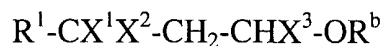


and



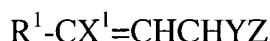
20
25 wherein X^2 , independently of X^1 , is F, Cl or Br.

7. The process of claim 6, wherein said aldehydes are together obtained by hydrolysis of an ether compound having the formula:

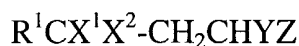


5 wherein X^3 , independent of X^1 and X^2 , is Cl, Br or I, and R^b is a straight chain or branched C_1 - C_6 alkyl group.

8. The process of claim 5, wherein the halogenated aliphatic- β -halo-carboxylic acids and halogenated aliphatic- α,β -saturated- β,β -dihalocarboxylic acids are formed by oxidation of an admixture of compounds having the formulae:



and



15 wherein X^2 , independently of X^1 , is F, Cl or Br; and

Y is OH when Z is M^1SO_3 , or Y is OR^b or OR^4 when Z is OR^4 , or Y and Z together form a $=NNHR^6$ group, a $=NHOR^7$ group or, a ring structure with the carbon to which they are attached having as members $-W^a-R^5-W^b$;

20 wherein M^1 is a cation selected from the group consisting of alkali metal cations, alkaline earth metal cations, NH_4^+ , $NR^2H_3^+$ and $NR^2R^3H_2^+$;

R^b is a straight chain or branched C_1 - C_6 alkyl group.

R^2 and R^3 are independently selected from the group consisting of straight chain and branched C_1 - C_6 alkyl, phenyl and phen C_1 - C_6 alkyl groups;

25 R^4 is selected from the group consisting of straight chain and branched C_1 - C_6 alkyl groups, straight chain and branched C_1 - C_6 alkyl groups substituted with one or

more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycles containing 5, 6 and 7 ring members, phenyl and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups;

5 R⁵ is selected from the group consisting of C₂-C₃ alkylene optionally substituted with straight chain, branched or cyclic C₁-C₆ alkyl groups, or C₂-C₃ alkylene optionally forming part of a 1,2-phenylene ring optionally ring-substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups;

 R⁶ is selected from the group consisting of straight chain and branched C₁-C₆ alkyl groups, straight chain and branched C₁-C₆ alkyl groups substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycles containing 5, 6 and 7 ring members, phenyl and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups;

15 R⁷ is selected from the group consisting of hydrogen, and straight chain and branched C₁-C₆ alkyl groups; and

 W^a and W^b are independently selected from the group consisting of O, N and S.

20 9. The process of claim 8, wherein Y is OH and Z is M¹SO₃, and said admixture of compounds is formed by reacting a bisulfite salt having the formula M¹HSO₃ with an ether compound having the formula:



25 wherein X³, independent of X¹ and X², is Cl, Br or I, and R^b is a straight chain or branched C₁-C₆ alkyl group.

10. The process of claim 8, wherein Y is OR^b or OR⁴, and Z is OR⁴, and said admixture of compounds is formed by reacting an alcohol having the formula R⁴OH with an ether compound having the formula:



wherein X³, independent of X¹ and X², is Cl, Br or I, and R^b is a straight chain or branched C₁-C₆ alkyl group.

11. The process of claim 8, wherein Y and Z together form a =NNHR⁶ group, and said admixture of compounds is formed by reacting a hydrazine compound having the formula NH₂NHR⁶ with an ether compound having the formula:



wherein X³, independent of X¹ and X², is Cl, Br or I, and R^b is a straight chain or branched C₁-C₆ alkyl group.

12. The process of claim 8, wherein Y and Z together form a =NOR⁷ group, and said admixture of compounds is formed by reacting a hydroxylamine having the formula NH₂OR⁷ with an ether compound having the formula:



25 wherein X³, independent of X¹ and X², is Cl, Br or I, and R^b is a straight chain or branched C₁-C₆ alkyl group.

13. The process of claim 8, wherein Y and Z together form a ring structure with the carbon to which they are attached having as members $-W^a-R^5-W^b-$; and said admixture of compounds is formed by reacting an compound having the formula $HW^a-R^5-W^bH$ with an ether compound having the formula:

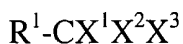
5



wherein X^3 , independent of X^1 and X^2 , is Cl, Br or I, and R^b is a straight chain or branched C_1 - C_6 alkyl group.

14. The process of claim 7, 9, 10, 11, 12 or 13, wherein said ether compound is prepared by reacting a 1,1,1-trihalogenated aliphatic compound having the formula:

15



with an unsaturated compound having the formula:

20



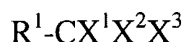
using UV light or transition metal catalysis.

15. A process for preparing an ether compound having the formula:

25



comprising reacting a 1,1,1-trihalogenated aliphatic compound having the formula:



with an unsaturated compound having the formula:



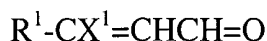
using UV light or transition metal catalysis, wherein R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups;

X^1 and X^2 are independently selected from the group consisting of F, Cl and Br, and X^3 is, independently of X^1 and X^2 , Cl, Br or I;

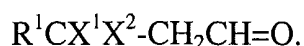
R^a is selected from the group consisting of hydrogen, straight chain and branched C_1 - C_6 alkyls, straight chain and branched C_1 - C_6 alkyls substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycle containing five, six and seven ring members, phenyl
15 and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C_1 - C_6 alkyl and C_1 - C_6 alkoxy; and

R^b is a straight chain or branched C_1 - C_6 alkyl group.

16. The process of claim 15, wherein R^a is hydrogen, and said process
20 further comprises the step of hydrolyzing said ether compound to form an admixture of aldehydes having the formulae:



and



25

17. The process of claim 15, wherein R^a is hydrogen, and said process further comprises the step of reacting said ether compound with a bisulfite salt having the formula M¹HSO₃ to form an admixture of compounds having the formulae:



wherein Y is OH, Z is M¹SO₃, M¹ is a cation selected from the group consisting of alkali metal cations, alkaline earth metal cations, NH₄⁺, NR²H₃⁺ and NR²R³H₂⁺, and R² and R³ are independently selected from the group consisting of straight chain and branched C₁-C₆ alkyl, phenyl and phen C₁-C₆ alkyl groups.

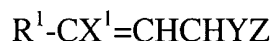
18. The process of claim 15, wherein R^a is hydrogen, and said process further comprises the step of reacting said ether compound with an alcohol having the formula R⁴OH to form an admixture of compounds having the formulae:



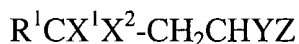
wherein Y is OR^b or OR⁴, Z is OR⁴ and R⁴ is selected from the group consisting of straight chain and branched C₁-C₆ alkyl groups, straight chain and branched C₁-C₆ alkyl groups substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycles containing 5, 6 and 7 ring members, phenyl and phenyl substituted with one or more groups

independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups.

19. The process of claim 15, wherein R^a is hydrogen, and said process further comprises the step of reacting said ether compound with a compound having the formula HW^a-R⁵-W^bH to form an admixture of compounds having the formulae:



and

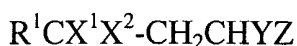


wherein Y and Z together form a ring structure with the carbon to which they are attached having as members -W^a-R⁵-W^b-; R⁵ is a C₂-C₃ alkylene optionally substituted with a straight chain, branched or cyclic C₁-C₆ alkyl group, or a C₂-C₃ alkylene forming part of 1,2-phenylene ring optionally substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups; and W^a and W^b are independently selected from the group consisting of O, N and S.

20. The process of claim 15, wherein R^a is hydrogen, and said process further comprises the step of reacting said ether compound with a hydrazine compound having the formula NH₂NHR⁶ to form an admixture of compounds having the formulae:



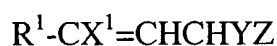
and



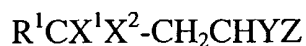
wherein Y and Z together form a =NNHR⁶ group, and R⁶ is selected from the group consisting of straight chain and branched C₁-C₆ alkyl groups, straight chain and

branched C₁-C₆ alkyl groups substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycles containing 5, 6 and 7 ring members, phenyl and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups.

21. The process of claim 15, wherein R^a is hydrogen, and said process further comprises the step of reacting said ether compound with a hydroxylamine compound having the formula NH₂OR⁷ to form an admixture of compounds having the formulae:

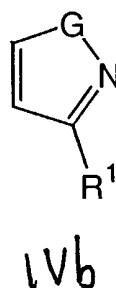
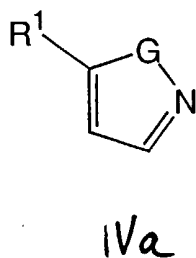


and



wherein Y and Z together form a =NOR⁷ group, and R⁷ is selected from the group consisting of hydrogen, and straight chain and branched C₁-C₆ alkyl groups.

22. The process of claim 20 or claim 21, additionally comprising the step of further heating said admixture to produce either the heterocyclic compound of Formula IVa or the heterocyclic compound of Formula IVb



wherein G is O or NR⁶.

23. The process of claim 1 or claim 15, wherein R^1 is a substituted or unsubstituted C_1 - C_{12} halogenated aliphatic radical.

24. The process of claim 23, wherein R^1 is fluorinated.

25. The process of claim 24, wherein R^1 is polyfluorinated.

26. The process of claim 25, wherein R^1 is perfluorinated.

27. The process of claim 23, wherein R^1 is substituted with one or more groups independently selected from the group consisting of C_1 - C_6 alkyls, C_1 - C_6 alkyl ethers, C_1 - C_6 alkyl esters and C_1 - C_6 alkenyls, each optionally containing one or more nitro, primary amino, secondary amino, cyano, hydroxyl, thiol or C_1 - C_6 alkylthiol groups.

28. The process of claim 23, wherein R^1 is selected from the group consisting of halogenated methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, n-heptyl, n-octyl or 2-ethylhexyl optionally further substituted with one or more groups independently selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, methane sulphonyl and cyano.

29. The process of claim 28, wherein R^1 is selected from the group consisting of C_1 - C_6 fluorinated alkyl radicals.

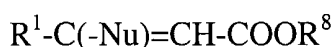
30. The process of claim 29, wherein R^1 is selected from the group consisting of fluoromethyl, difluoromethyl, trifluoromethyl, fluorethyl, difluoroethyl,

trifluoroethyl, pentafluoroethyl, perfluoropropyl, perfluorobutyl, perfluoropentyl and perfluorohexyl groups.

31. The process of claim 30, wherein R^1 is a trifluoromethyl group.

5

32. A compound having the formula:



wherein R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups;

Nu is a nucleophile moiety; and

R^8 is selected from the group consisting of hydrogen, straight chain and branched C_1 - C_6 alkyl groups, NH_4^+ , $R^2NH_3^+$, alkali metal ions, alkaline earth metal ions, Cl, NH_2 , NHR^2 , $NHNHR^2$, CN, SH and SR^2 , wherein R^2 is selected from the group consisting of straight chain or branched C_1 - C_6 alkyl groups, phenyl and phenyl C_1 - C_6 alkyl groups.

15

33. The compound of claim 32, wherein Nu is selected from the group consisting of F, Cl, Br, I, straight chain, branched and cyclic C_1 - C_{12} alkoxy groups, phenoxy, substituted phenoxy groups, straight chain, branched and cyclic C_1 - C_{12} alkylamido groups, thiol, straight chain, branched and cyclic C_1 - C_{12} alkylthiol groups, arylthiol groups, acyloxy, cyano, azo, cyanate and thiocyanate.

20

34. The compound of claim 32, wherein Nu is an amino group having the formula NR^9R^{10} , wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen and straight chain and branched C_1 - C_6 alkyl groups.

25

35. A compound having the formula:



5 wherein R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups;

X^1 and X^2 are independently selected from the group consisting of F, Cl and Br, and X^3 , independently of X^1 and X^2 , is Cl, Br or I;

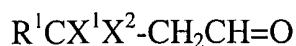
R^a is selected from the group consisting of hydrogen, straight chain and branched C_1 - C_6 alkyls, straight chain and branched C_1 - C_6 alkyls substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycle containing five, six and seven ring members, phenyl and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C_1 - C_6 alkyl and C_1 - C_6 alkoxy; and

15 R^b is a straight chain or branched C_1 - C_6 alkyl group.

36. A compound selected from the group consisting of:



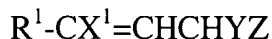
20 and



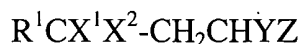
wherein R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups; and

25 X^1 and X^2 are independently selected from the group consisting of F, Cl and Br.

37. A compound selected from the group consisting of:



and



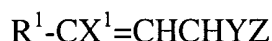
wherein Y is OH, Z is M^1SO_3 , and M^1 is a cation selected from the group consisting of alkali metal cations, alkaline earth metal cations, NH_4^+ , $NR^2H_3^+$ and $NR^2R^3H_2^+$;

R^2 and R^3 are independently selected from the group consisting of straight chain and branched C_1 - C_6 alkyl, phenyl and phen C_1 - C_6 alkyl groups;

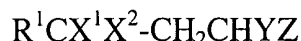
R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups; and

X^1 and X^2 are independently selected from the group consisting of F, Cl and Br.

38. A compound selected from the group consisting of:



and

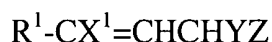


wherein Y is OR^b or OR^4 , Z is OR^4 ; R^b is a straight chain or branched C_1 - C_6 alkyl group; and R^4 is selected from the group consisting of straight chain and branched C_1 - C_6 alkyl groups, straight chain and branched C_1 - C_6 alkyl groups substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycles containing 5, 6 and 7 ring members, phenyl and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C_1 - C_6 alkyl groups and C_1 - C_6 alkoxy groups;

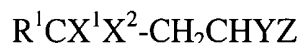
R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups; and

X^1 and X^2 are independently selected from the group consisting of F, Cl and Br.

5 39. A compound selected from the group consisting of:



and



wherein Y and Z together form a ring structure with the carbon to which they are attached having as members $-W^a-R^5-W^b-$;

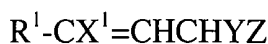
R^5 is a C_2 - C_3 alkylene optionally substituted with a straight chain, branched or cyclic C_1 - C_6 alkyl group, or a C_2 - C_3 alkylene forming part of 1,2-phenylene ring
15 optionally substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C_1 - C_6 alkyl groups and C_1 - C_6 alkoxy groups

W^a and W^b are independently selected from the group consisting of O, N and S;

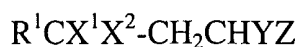
R^1 is selected from the group consisting of straight chain and branched halogenated C_1 - C_{12} aliphatic groups; and

20 X^1 and X^2 are independently selected from the group consisting of F, Cl and Br.

40. A compound selected from the group consisting of:



and



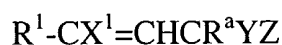
25

wherein Y and Z together form a =NNHR⁶ group, and R⁶ is selected from the group consisting of straight chain and branched C₁-C₆ alkyl groups, straight chain and branched C₁-C₆ alkyl groups substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycles containing 5, 6 and 7 ring members, phenyl and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups;

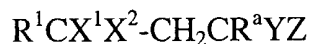
R¹ is selected from the group consisting of straight chain and branched halogenated C₁-C₁₂ aliphatic groups; and

X¹ and X² are independently selected from the group consisting of F, Cl and Br.

41. A compound selected from the group consisting of:



and

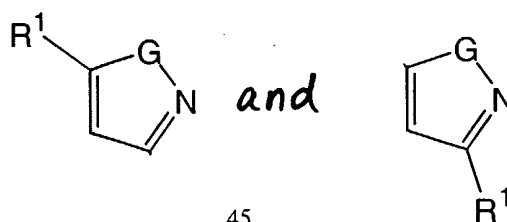


wherein Y and Z together form a =NOR⁷ group, and R⁷ is selected from the group consisting of hydrogen, and straight chain and branched C₁-C₆ alkyl groups;

R¹ is selected from the group consisting of straight chain and branched halogenated C₁-C₁₂ aliphatic groups; and

X¹ and X² are independently selected from the group consisting of F, Cl and Br.

42. A compound selected from the group consisting of:



wherein G is O or NR⁶ and R⁶ is selected from the group consisting of straight chain and branched C₁-C₆ alkyl groups, straight chain and branched C₁-C₆ alkyl groups substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido and nitrogen heterocycles containing 5, 6 and 7 ring members, phenyl and phenyl substituted with one or more groups independently selected from the group consisting of halo, cyano, nitro, amido, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups; and

R¹ is selected from the group consisting of straight chain and branched halogenated C₁-C₁₂ aliphatic groups.

43. The compound of claim 32, 35, 36, 37, 38, 39, 40 or 41, wherein R¹ is a substituted or unsubstituted C₁-C₁₂ halogenated aliphatic radical.

44. The compound of claim 43, wherein R¹ is fluorinated.

45. The compound of claim 44, wherein R¹ is polyfluorinated.

46. The compound of claim 45, wherein R¹ is perfluorinated.

47. The compound of claim 43, wherein R¹ is substituted with one or more groups independently selected from the group consisting of C₁-C₆ alkyls, C₁-C₆ alkyl ethers, C₁-C₆ alkyl esters and C₁-C₆ alkenyls, each optionally containing one or more nitro, primary amino, secondary amino, cyano, hydroxyl, thiol or C₁-C₆ alkylthiol groups.

48. The compound of claim 43, wherein R^1 is selected from the group consisting of halogenated methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, n-heptyl, n-octyl or 2-ethylhexyl optionally further substituted with one or more groups independently selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, methane sulphonyl and cyano.

49. The compound of claim 48, wherein R^1 is selected from the group consisting of C_1 - C_6 fluorinated alkyl radicals.

50. The compound of claim 49, wherein R^1 is selected from the group consisting of fluoromethyl, difluoromethyl, trifluoromethyl, fluorethyl, difluoroethyl, trifluoroethyl, pentafluoroethyl, perfluoropropyl, perfluorobutyl, perfluoropentyl and perfluorohexyl groups.

51. The compound of claim 50, wherein R^1 is a trifluoromethyl group.

52. The compound of claim 42, wherein R^1 is a substituted or unsubstituted C_1 - C_{12} halogenated aliphatic radical.

53. The compound of claim 52, wherein R^1 is fluorinated.

54. The compound of claim 53, wherein R^1 is polyfluorinated.

55. The compound of claim 54, wherein R^1 is perfluorinated.

56. The compound of claim 52, wherein R¹ is substituted with one or more groups independently selected from the group consisting of C₁-C₆ alkyls, C₁-C₆ alkyl ethers, C₁-C₆ alkyl esters and C₁-C₆ alkenyls, each optionally containing one or more nitro, primary amino, secondary amino, cyano, hydroxyl, thiol or C₁-C₆ alkylthiol groups.

57. The compound of claim 52, wherein R¹ is selected from the group consisting of halogenated methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, n-heptyl, n-octyl or 2-ethylhexyl optionally further substituted with one or more groups independently selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, methane sulphonyl and cyano.

58. The compound of claim 57, wherein R¹ is selected from the group consisting of C₁-C₆ fluorinated alkyl radicals.

59. The compound of claim 58, wherein R¹ is selected from the group consisting of fluoromethyl, difluoromethyl, trifluoromethyl, fluorethyl, difluoroethyl, trifluoroethyl, pentafluoroethyl, perfluoropropyl, perfluorobutyl, perfluoropentyl and perfluorohexyl groups.

60. The compound of claim 59, wherein R¹ is a trifluoromethyl group.